

Early Changes in Plasma and Urinary Potassium in Diuretic-Treated Patients with Systemic Hypertension

VASILIOS PAPADEMETRIOU, MD, MICHAEL PRICE, MD, ELIZABETH JOHNSON, RN,
MARLENE SMITH, RN, and EDWARD D. FREIS, MD

Two groups of patients with uncomplicated systemic hypertension were studied. Group 1 included 11 patients who had overt hypokalemia with diuretic drug treatment, and group 2 included 11 patients who remained normokalemic. After baseline studies without treatment were performed, both groups received hydrochlorothiazide, 50 mg twice daily. Plasma potassium (PK) was significantly reduced within the first day of treatment and stabilized by day 7 in both groups. The average decrease in PK was 1.0 ± 0.1 mEq/liter ($p < 0.01$) in the first group and 0.6 ± 0.2 mEq/liter ($p < 0.01$) in the second group. Cumulative losses of K were approximately 200 mEq in the hypokalemic group and were minimal in

the normokalemic group as assessed by 24-hour urinary collections. Patients in the hypokalemic group also had a greater reduction in body weight and blood pressure. Supplementation with KCl, 96 mEq/day, or triamterene, 200 mg/day, in 9 hypokalemic patients resulted in an increase of PK to approximately 3.5 mEq/liter leveling off by day 7, and a cumulative K retention of approximately 200 mEq. Thus, overt thiazide-induced hypokalemia was associated with small and biologically unimportant losses of K from body stores. With replacement therapy the estimated amount of retained K was also small.

(Am J Cardiol 1984;54:1015-1019)

Diuretic-induced hypokalemia has been a matter of major concern, leading often to the routine use of potassium chloride (KCl) supplements and K-sparing diuretic therapy. For example, in 1981 more than 7.5 million prescriptions for KCl and 19 million prescriptions for K-sparing diuretic drugs were prescribed for patients with hypertension, at a cost exceeding \$250 million.¹

Hypokalemia, defined as plasma potassium (PK) ≤ 3.5 mEq/liter, occurs in approximately 20% of patients with essential hypertension who receive diuretic therapy.^{2,3} However, severe hypokalemia (PK < 3.0 mEq/liter) occurs in only a small percentage.^{4,5} Whether the hypokalemia reflects a true deficit of total body K is controversial. Some investigators⁶ found significant decreases in the total body K with diuretic treatment, whereas others found minimal reductions with long-term diuretic treatment.⁷⁻¹⁰ Total body K remained unchanged when KCl supplements were added to diuretic therapy.^{8,11} Although numerous studies have

shown that diuretic therapy results in a mild decrease of PK⁷⁻¹¹ and an initial increase in urinary K excretion,^{12,13} studies assessing the duration and severity of kaliuresis in patients with overt hypokalemia are scarce.

This study investigated 2 groups of hypertensive patients. The first group included patients known to have overt hypokalemia (PK ≤ 3.2 mEq/liter) when receiving diuretic therapy. The second group maintained normal PK (≥ 3.5 mEq/liter) when receiving diuretic therapy. The following questions were studied: (1) Are there any differences between these 2 groups in blood pressure (BP) response, fluid loss or electrolyte excretion in the urine? (2) How rapidly does hypokalemia occur and how much K is lost in the urine? (3) In the hypokalemic patients, when large doses of KCl supplements or K-sparing diuretic drugs are added, how much K is retained and how soon is hypokalemia corrected?

Methods

Patients: Twenty-two patients with mild to moderate hypertension uncomplicated by heart or renal disease were studied. Eleven of these patients had overt hypokalemia while receiving therapy, whereas the other 11 remained normokalemic. All patients were black. The average age was 54 ± 3

From the Veterans Administration and Georgetown University Medical Centers, Washington, D.C. Manuscript received April 26, 1984; revised manuscript received July 6, 1984, accepted July 20, 1984.

Address for reprints: Vasilios Papademetriou, MD, Hypertension Research, Veterans Administration Medical Center, 50 Irving Street, N.W., Washington, D.C. 20422.

TABLE I Control Data Before Diuretic Treatment

Variables	Normokalemic Patients	Hypokalemic Patients
Age (yr)	54 ± 3	56 ± 2
Body weight (Kg)	85 ± 5	90 ± 4
Blood pressure		
Systolic (mm Hg)	150 ± 6	152 ± 7
Diastolic (mm Hg)	97 ± 6	99 ± 4
Heart rate	74 ± 4	77 ± 4
Plasma K (mEq/liter)	4.4 ± 0.1	3.9 ± 0.1*
Plasma Na (mEq/liter)	143 ± 1	141 ± 1
Plasma Cl (mEq/liter)	108 ± 2	105 ± 9
Plasma creatinine (mg/dl)	1.2 ± 0.1	1.2 ± 0.1
Urine volume (ml/24 hr)	1,606 ± 140	1,405 ± 108
Urine K (mEq/24 hr)	49 ± 8	58 ± 7
Urine Na (mEq/24 hr)	183 ± 28	196 ± 24
Urine Cl (mEq/24 hr)	198 ± 30	203 ± 32
Urine creatinine (g/24 hr)	1.8 ± 0.1	1.9 ± 0.1
Creatinine clearance (ml/min)	103 ± 5	112 ± 6

Values are mean ± standard error of the mean.

* Average baseline PK values were significantly different, $p < 0.01$; for all other values, the difference was not significant.

years in the normokalemic group and 56 ± 3 years in the hypokalemic group (mean ± standard error of the mean). Twenty patients were treated with a diuretic drug alone, 1 received metoprolol and the other received methyldopa in addition to a diuretic drug. In the latter 2 patients, the dosage of methyldopa and metoprolol remained unchanged throughout the study.

Study protocol: The study was conducted in 4 phases: baseline, diuretic, diuretic plus KCl and diuretic plus triamterene. Only the hypokalemic patients proceeded to the third and fourth phase. At each visit the following data were collected: sitting BP, heart rate, body weight, plasma and 24-hour urine, creatinine, K, sodium and chloride. At each visit the patient brought with him the urine that had been collected during the preceding 24 hours.

Screening phase: Diuretic treatment was discontinued for at least 2 weeks and the patients were given KCl, 20 mEq twice daily, for the first 5 days in order to restore any existing

K deficits. Baseline data were collected at the end of this period.

Diuretic phase: After the baseline studies, treatment with hydrochlorothiazide (HCTZ), 50 mg twice daily, was begun and the patients were seen on days 1, 3, 7, 14 and 28 of diuretic treatment. After completing the 4-week period with diuretic treatment, patients whose PK was reduced to ≤ 3.2 mEq/liter proceeded to the next phase. If a patient had hypokalemic symptoms or a PK of ≤ 2.6 , therapy with KCl was begun earlier without completing the 4-week period with diuretic drugs alone.

Diuretic plus KCl phase: Nine patients from the hypokalemic group proceeded to the diuretic plus KCl phase. In addition to the diuretic drug, these patients received 96 mEq/day of supplementary KCl in wax matrix tablets ("slow K"). They were examined and blood and urine were collected on days 1, 3, 7, 14 and 28 of this phase.

Diuretic plus triamterene phase: After the diuretic plus KCl phase, KCl was discontinued. Patients then received diuretic therapy alone for a period of time sufficient to allow hypokalemia to recur (15 ± 3 days). After this second baseline period the patients were given triamterene, 100 mg twice daily, and were seen again on days 1, 3, 7, 14 and 28 of this phase.

Results were analyzed using the Student *t* test for paired observations. The study protocol was approved by the Research and Development Committee of the Veterans Administration Medical Center at Washington, D.C., and all patients gave informed written consent.

Results

At baseline, the average BP was 150/97 mm Hg in the normokalemic group and 152/99 mm Hg in the hypokalemic group (Table I). Plasma and urinary electrolytes and plasma creatinine levels were within normal limits in both groups. However, the average baseline PK was significantly lower in the group that became hypokalemic while receiving diuretic therapy (3.9 ± 0.1 vs 4.4 ± 0.1 , $p < 0.01$).

The mean 24-hour urinary creatinine excretion and the average urinary volume indicated adequate urine

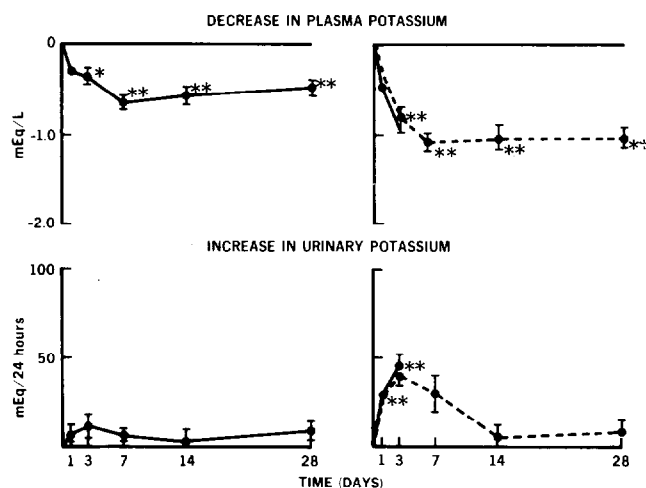


FIGURE 1. Changes in plasma and 24-hour urinary potassium levels during the diuretic treatment alone. Left, changes in the group of patients who remained normokalemic; right, changes that occurred in the hypokalemic group. Dotted lines represent mean ± standard error of the mean in the 7 patients who completed 4 weeks with hydrochlorothiazide therapy. Solid lines represent mean ± standard error of the mean of 11 patients. * $p < 0.05$; ** $p < 0.01$.

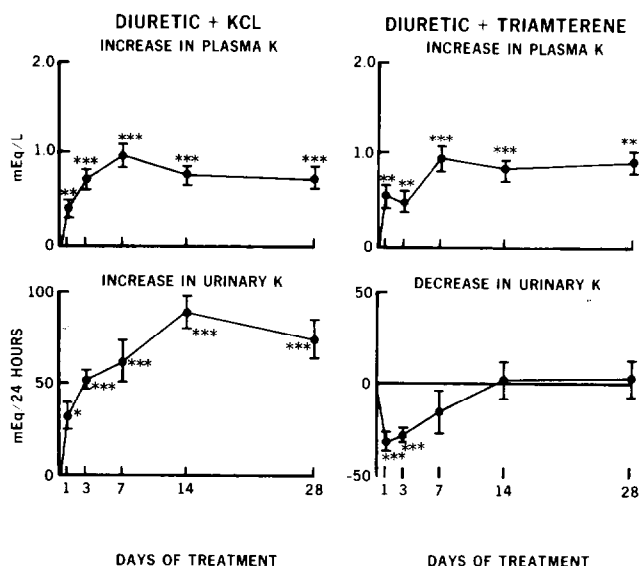


FIGURE 2. Changes in plasma and 24-hour urinary potassium in 9 hypokalemic patients who received replacement therapy. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

collections. The average creatinine clearance during this control period was 103 ± 5 ml/min in the normokalemic group and 112 ± 7 ml/min in the hypokalemic group.

Diuretic phase only: Figure 1 shows the changes in plasma and 24-hour urinary K during the diuretic phase in both groups of patients. In the normokalemic group, PK decreased by 0.6 ± 0.1 mEq/liter ($p < 0.01$) on day 7 of diuretic treatment and stabilized thereafter. In the hypokalemic group, PK decreased 0.4 ± 0.1 mEq/liter ($p < 0.05$) on day 1 of diuretic treatment and by day 3 PK was 1.0 ± 0.2 mEq/liter lower than the baseline value ($p < 0.001$). Two of these patients exhibited a PK of 2.3 and 2.6 mEq/liter, respectively, on day 3 and therapy with KCl was begun. On day 7 of diuretic treatment, 1 more patient was found with a PK of 2.5 mEq/liter while on day 14 another patient had a PK level of 2.4 mEq/liter. These 2 patients also began therapy with KCl before completing the full 4-week period with diuretic drugs alone. Thus, only 7 of the 11 patients completed the full 4 weeks of treatment (Fig. 1). After day 7, PK levels remained relatively stable.

There was no increase in the 24-hour urinary excretion of K in the group of patients who remained normokalemic after HCTZ treatment. In the hypokalemic group, the urinary excretion of K increased by 26 ± 8 mEq/24 hours ($p < 0.05$) during the first day of treatment and by 41 ± 8 mEq/24 hours ($p < 0.001$) on the third day. On day 7, the 24-hour urinary K excretion was higher, but was not significantly different from baseline values. It was estimated that the total net loss of K from body stores probably did not exceed 200 mEq.

Addition of KCl: The left panel of Figure 2 shows the changes of plasma and 24-hour urinary K when KCl, 96 mEq/day in divided doses, was added to the regimen of 9 hypokalemic patients. The average PK in patients receiving diuretic treatment alone, before KCl was initiated, was 2.8 ± 0.1 mEq/liter. The average PK increased by 0.4 ± 0.2 mEq/liter on day 1 and by 0.7 ± 0.2 mEq/liter on day 3 of KCl treatment. PK reached its highest level of 3.8 ± 0.2 mEq/liter on day 7, leveling off thereafter. All patients were compliant, as judged by pill counts, which indicated they had taken an average of 80 mEq/day. The difference between the 80-mEq intake and the increase in urinary excretion of K represented retained K. This indicated (Fig. 2) that approximately 50 mEq of K were retained on day 1 of KCl treatment, about 30 mEq/day from days 2 to 3 and approximately 20 mEq/day from days 4 to 7. Thereafter, essentially all of the administered K was excreted in the urine. Thus, the net total quantity of K retained during this period probably did not exceed 200 mEq.

Addition of triamterene: After the second phase of the study, KCl was discontinued. Patients continued taking HCTZ alone, which resulted in return of overt hypokalemia (15 \pm 3 days). The average PK with diuretic therapy alone, before triamterene was 2.7 ± 0.1 mEq/liter and the average urinary K excretion was 53 mEq/24 hours. As shown on the right panel in Figure 2, PK increased on day 1 of the triamterene treatment by 0.5 mEq/liter, from 2.7 ± 0.1 to 3.2 mEq/liter ($p < 0.01$). On day 3 PK averaged 3.2 ± 0.1 mEq/liter and by day 7 it stabilized at about 3.5 to 3.6 mEq/liter. The average

K retention was 30 ± 4 mEq/24 hours greater than baseline ($p < 0.001$) on day 3 and 13 ± 6 mEq/24 hours on the seventh day (difference not significant). On days 14 and 28 of triamterene treatment, the urinary excretion of K was almost identical with the HCTZ control. Again, it can be estimated that the cumulative net retention of K during the HCTZ plus triamterene phase probably did not exceed 200 mEq.

Sodium excretion, body weight, blood pressure and creatinine: Figure 3 shows the changes in 24-hour urinary excretion of sodium, body weight, BP and plasma creatinine during the diuretic-alone phase in both groups and the diuretic plus triamterene phase in the hypokalemic group. No changes in the above occurred during KCl treatment and therefore these data are not shown. The 24-hour urinary excretion of sodium was significantly increased in both groups only on the first day of diuretic treatment (Fig. 3). The decrease in body weight from baseline was 1.2 ± 0.1 kg ($p < 0.01$) in the normokalemic group and 2.1 ± 0.1 kg ($p < 0.001$) in the hypokalemic group, and stabilized on day 3 of diuretic treatment. The average BP was significantly reduced in both groups. There was a small but statistically significant increase in plasma creatinine levels in both

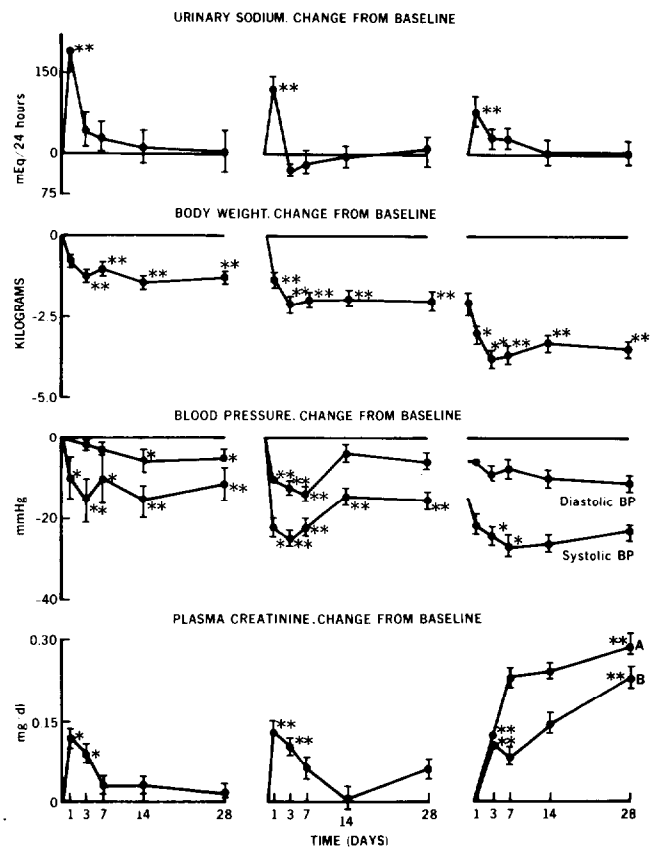


FIGURE 3. Mean (\pm standard error of the mean) changes in urinary sodium, body weight blood pressure and plasma creatinine. **Left**, diuretic-alone phase in the normokalemic group; **middle**, diuretic-alone phase in the hypokalemic group; **right**, diuretic plus triamterene phase in 9 hypokalemic patients. A = change in plasma creatinine for all 9 patients; B = change in plasma creatinine in the 8 patients excluding the patient with the greatly elevated plasma creatinine; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

TABLE II Mean Reductions in Plasma Potassium Body Weight and Blood Pressure on Day 7 of Hydrochlorothiazide Treatment

	Normokalemic Patients	Hypokalemic Patients	p Value
Plasma potassium (mEq/liter)	0.6 ± 0.1	1.0 ± 0.1	<0.05
Body weight (kg)	1.1 ± 0.3	2.2 ± 0.4	<0.05
Systolic BP (mm Hg)	15 ± 3	22 ± 5	NS
Diastolic BP (mm Hg)	6 ± 2	12 ± 3	p < 0.05

Values are mean ± standard error of the mean.
BP = blood pressure; NS = not significant.

groups during the first 3 days of diuretic treatment, but thereafter it returned to baseline. Table II compares the changes in PK, body weight and BP between the 2 groups on the seventh day of diuretic treatment, because by that day most variables stabilized. The decrease in PK was significantly greater, as expected, in the hypokalemic group, 1.0 ± 0.1 vs 0.6 ± 0.1 mEq/liter (p < 0.05). However, there was also a significantly greater reduction in body weight and diastolic BP in the hypokalemic group (Table II).

The addition of triamterene to HCTZ resulted in further changes in sodium excretion, body weight, BP and plasma creatinine level. The p values shown in Figure 3 compare the values before and after the addition of triamterene. Sodium excretion increased by 76 ± 18 mEq (p < 0.01) during the first 24 hours of treatment with triamterene. The sodium excretion levels remained somewhat, but not significantly, higher than that in the preceding period with HCTZ treatment alone until day 7. Body weight was correspondingly reduced by 1.7 ± 0.2 kg (p < 0.01) on day 3, after which it remained stable. Although diastolic BP did not change, systolic BP was further reduced with the addition of triamterene.

Plasma creatinine also increased. One patient had marked elevation of plasma creatinine from 1.6 to 3.1 mg/dl on day 7, which receded to 2.7 mg/dl on day 14 and to 2.3 mg/dl on day 28 of triamterene treatment. Curve A in Figure 3 represents the change in plasma creatinine for all 9 patients and curve B, the change for the 8 patients excluding the patient with the markedly elevated plasma creatinine. The average plasma creatinine level was significantly elevated during treatment with triamterene and remained so to the twenty-eighth day of treatment. This was in contrast to HCTZ alone, which was associated with only a transient increase.

As shown in Table III, KCl or triamterene, even in relatively large doses, normalized PK in only approximately half of the patients. At the end of the KCl phase, as at the end of the triamterene phase, only 5 of 9 patients had a normal level of PK (≥3.5 mEq/liter).

Discussion

One of the objectives in this study was to identify differences between the patients who maintain normal PK with diuretic therapy and those who become overtly hypokalemic. The 2 groups of patients were therefore selected on the basis of their known PK response to

TABLE III Number of Patients with Normalized Plasma Potassium (≥3.5 mEq/liter) on Each Day of Treatment

	Days					
	0	1	3	7	14	28
Potassium chloride	0	1	5	6	4	5
Triamterene	0	3	2	4	4	5

diuretic drugs, but were comparable in other respects (Table I). However, the average baseline PK level in the patients who became hypokalemic was significantly lower than that in patients who maintained their PK levels within the normal range during thiazide therapy.

Although the hypokalemic subjects started from a lower baseline PK than the normokalemic group, they also exhibited an absolute decrement in PK that was considerably greater than that in the normokalemic patients. The hypokalemic group also exhibited a greater reduction in body weight and diastolic BP. Diuretic treatment in the hypokalemic group also was associated with an average loss of about 200 mEq of K in the urine, whereas no detectable increase was observed in the normokalemic group.

A possible explanation for the observed differences is that the hypokalemic patients had a greater response to diuretic therapy as indicated by BP and body weight changes. Greater diuresis made available more sodium in the distal nephron to be exchanged with K, which in turn would explain the greater increase in the 24-hour urinary excretion of K that occurred in the hypokalemic group.

Although 24-hour urine samples were not obtained every day, there was a sufficient number collected at strategic points to estimate the total net losses of body K with thiazides. The loss even in the hypokalemic group was small, averaging approximately 200 mEq. Because total body K approximates 4,000 mEq,⁴ thiazide treatment resulted in an average total body K loss of about 5%. Maronde et al¹³ also found that the K losses occurred during the first 3 days of diuretic therapy and were less than 300 mEq. Kassirer and Harrington⁴ reviewed the pertinent published reports and concluded that the decrease in total body K due to diuretic therapy is small, even after long-term continuous treatment with thiazides.

The hypokalemic patients in this study were selected on the basis of exhibiting overt hypokalemia during thiazide treatment. The dose of 50 mg of HCTZ twice daily is more conducive to the development of hypokalemia than are smaller doses. However, despite this dosage and the relatively large decreases in PK, reductions in total body K were small. Therefore, even in this selected group with extracellular K reduced by more than 25%, thiazide-induced hypokalemia did not reflect a major deficit of total body K.

These observations suggest that there is a change in the equilibrium between extracellular and intracellular concentrations of K, which could result in part from alkalosis and volume loss.^{14,15} Both volume reduction

and alkalosis, consequences of thiazide diuretic therapy, can reduce extracellular but not intracellular K, resulting in hypokalemia. This mechanism is more apparent in the normokalemic group, in which PK decreased by an average of 0.6 mEq/liter despite no net increase in urinary K.

The addition of KCl in hypokalemic patients tended to reverse the hypokalemia and restored the small losses in total body K. The average PK increased significantly and the estimated gain in total body K approximated 200 mEq. Both changes occurred during the first week of replacement therapy. After the first week, most of the administered KCl was excreted in the urine. However, despite the relatively large dose of KCl—96 mEq/day—4 of the 9 patients remained hypokalemic (PK <3.5 mEq/liter) at the end of 4 weeks of replacement therapy. Other investigators using smaller doses of 30 to 40 mEq/day of KCl failed to find an increase in either plasma or total body K.^{8,11} Despite persistent hypokalemia, these patients appeared to excrete most of the administered KCl in the urine.

A similar pattern was observed when triamterene, instead of KCl, was added to patients with hypokalemia. The average PK increased to nearly normal levels during the first week of treatment, and this was associated with an estimated net gain of about 200 mEq of total body K. Changes during the subsequent 3 weeks of treatment were minor or nonexistent. As occurred with KCl replacement therapy, 4 patients continued to exhibit hypokalemia despite daily doses of 200 mg of triamterene. Such results suggest that entirely normal levels of PK may not be attained even after the small net losses of K are replaced, again suggesting that the hypokalemia resulting from thiazide diuretic therapy is not associated with a major deficit in body stores.

Unlike the transient increase seen with HCTZ, the addition of triamterene in 9 hypokalemic patients was associated with further sustained increase in plasma creatinine. Mild but significant increase of plasma

creatinine has been reported.^{16,17} Triamterene has been reported to cause acute reversible renal failure when combined with indomethacin,¹⁸ and has also been identified as being present in renal calculi.¹⁹

References

1. Harrington JT, Isner JM, Kassirer JP. Our national obsession with potassium. *Am J Med* 1982;73:155-159.
2. Gifford RW, Mattox VR, Orvis AL, Sones DA, Rosevar JW. Effects of thiazide diuretics on plasma volume, body electrolytes and excretion of aldosterone in hypertension. *Circulation* 1961;24:1197-1205.
3. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. III. Influence of age, diastolic pressure, and prior cardiovascular disease: further analysis of side effects. *Circulation* 1972;65:991-1004.
4. Kassirer JP, Harrington JT. Diuretics and potassium metabolism: a reassessment of the need, effectiveness and safety of potassium therapy. *Kidney Int* 1977;2:505-515.
5. Morgan DB, Davidson C. Hypokalemia and diuretics: an analysis of publications. *Br Med J* 1980;1:905-908.
6. Edmonds CJ, Jasani B. Total body potassium in hypertensive patients during prolonged diuretic therapy. *Lancet* 1982;2:8-12.
7. Dargie HJ, Boddy K, Kennedy AC, King PC, Read PR, Ward DM. Total body potassium in long-term frusemide therapy: is potassium supplement necessary? *Br Med J* 1984;2:316-319.
8. Leemhuis MP, VanDamme KJ, Struyrenberg A. Effects of chlorthalidone on serum and total body potassium in hypertensive patients. *Acta Med Scand* 1976;200:37-45.
9. Wilkinson PR, Hesp R, Issler H, Raftery EB. Total body and serum potassium during prolonged thiazide therapy for essential hypertension. *Lancet* 1975;1:759-762.
10. Wilkinson PR. Potassium changes during diuretic therapy. *Cardiovasc Med* 1978;1:181-183.
11. Down PF, Polak A, Rao R, Mead JA. Fate of potassium supplements in six out patients receiving long-term diuretics for oedematous disease. *Lancet* 1972;2:721-724.
12. Freis ED, Wanko A, Wilson IM, Parrish AE. Chlorothiazide in hypertensive and normotensive patients. *Ann NY Acad Sci* 1958;71:450-55.
13. Maronde RF, Milgrom M, Dickey JM. Potassium loss with thiazide therapy. *Amer Heart J* 1969;78:16-21.
14. Taiso PJ, Carballo AJ. Effects of benzothiadiazines on serum and total body electrolytes. *Ann NY Acad Sci* 1960;88:822-840.
15. Anderson J, Godfrey BE, Hill DM, Munrofaure AD, Sheldon J. A comparison of the effects of hydrochlorothiazide and of frusemide in the treatment of hypertensive patients. *Quart J Med* 1971;15:541-560.
16. DeCarvalho GR, Emory AC, Frohlich ED. Spironolactone and triamterene in volume-dependent essential hypertension. *Clin Pharmacol Ther* 1980;27:53-56.
17. Walker BR, Hoppe RC, Alexander F. Effects of triamterene on the renal clearance of calcium magnesium, phosphate and uric acid. *Clin Pharmacol Ther* 1972;13:245-250.
18. Favre L, Glasson P, Vallotton MB. Reversible acute renal failure from combined triamterene and indomethacin. *Ann Intern Med* 1982;96:317-320.
19. Ettinger B, Oldroyd NO, Sorgel F. Triamterene nephrolithiasis. *JAMA* 1980;244:2443-2445.